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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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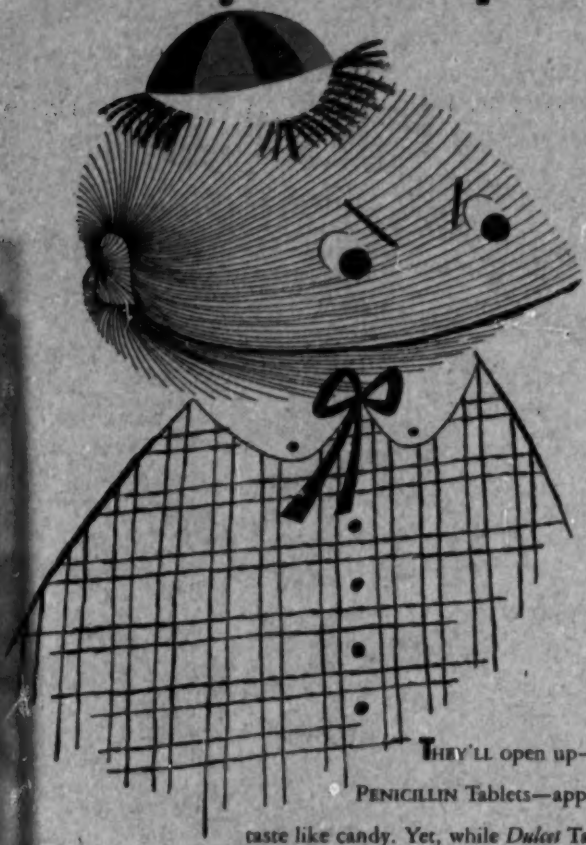

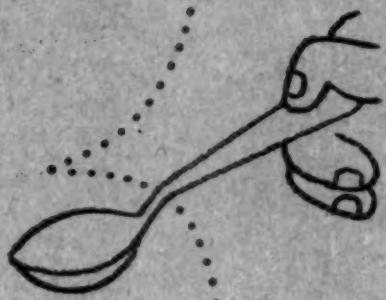

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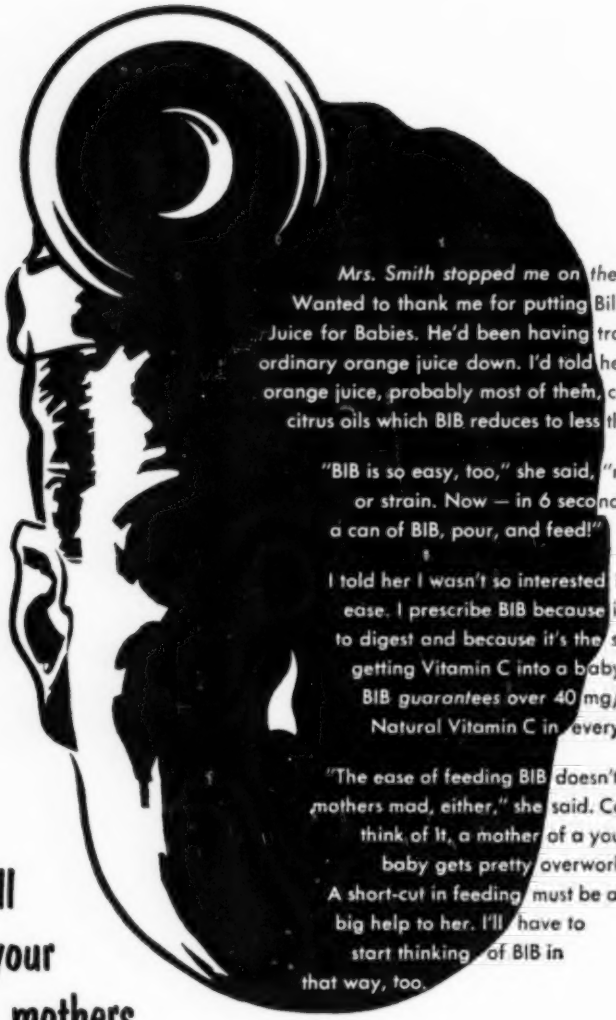

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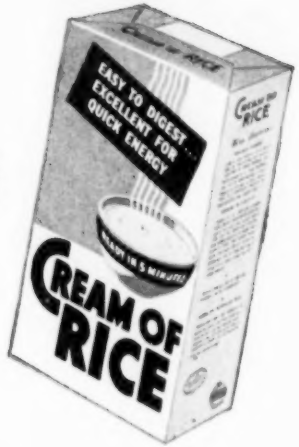

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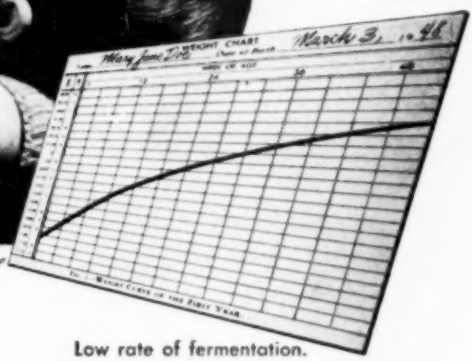

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Peel oil, previously shown to cause allergic response and poor tolerance, especially in infants,[4] is held to an arbitrary minimum in Minute Maid. Samples of home-squeezed juice expressed by typical housewives showed peel oil contents up to 700% higher than Minute Maid.

Bacterial counts were found to be as high as 350,000 per ml. in home-squeezed samples—but were uniformly low in Minute Maid. Technicians ascribe this to the combination of rigid sanitary controls in the Minute Maid process and the low pH and low temperatures at which the juice is kept. In the case of home-squeezed juice, high bacterial counts are doubtless due to contamination from the exterior peel which is unknowingly added to the juice during preparation.

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GUILLAIN-BARRÉ SYNDROME*

REPORT OF CASE FOLLOWING MEASLES

I. BLANCHE BOURNE, M.D.

AND

ROLAND B. SCOTT, M.D.

Washington, D. C.

The Guillain-Barré syndrome was once thought to be rare in children. However, an increasing number of cases are being reported.[1-6] The condition is important because of the differential diagnosis and favorable prognosis. The following case is that of a child in whom the Guillain-Barré syndrome followed an attack of measles.

CASE REPORT

E. B., a 5½-year-old male, entered Freedmen's Hospital on March 25, 1950 with the complaints of irritability, drowsiness and inability to walk. On March 10, 1950, the patient developed measles. On the seventh day following the onset of measles, he became irritable and complained of dizziness and headaches. He exhibited drowsiness during the day and insomnia at night. Upon attempting to walk, stumbling and ataxia were noted. Incontinence of urine was present. Four days prior to admission, weakness of the lower extremities was observed. The condition progressed until he was practically unable to walk and hospitalization was advised.

This child had uncomplicated chickenpox and pertussis at 8

*From the Department of Pediatrics, Howard University School of Medicine and the Pediatric Service of Freedmen's Hospital, Washington, D. C.

months. The developmental history was normal. A 9-month-old sibling was ill at home with measles at the time this patient entered the hospital.

Physical examination on admission revealed temperature 98.6° F., pulse 100, respiration 24, blood pressure 128/80. The child was well-developed and well-nourished. He was fully conscious and did not appear acutely ill. However, he was uncooperative in the examination, querulous, and complained of pain whenever the extremities were handled. The pupils were equal and reacted normally to light and accommodation. Fundoscopic examination showed retinal hyperemia and elevation of the surface of both discs, with loss of boundaries and blurring of structures. The pharynx was injected. The chest was symmetrical, expansion bilaterally equal and respiratory rate regular. The lungs, heart and abdomen were all essentially negative. The muscle tone of the extremities appeared good. Upon attempting to walk there was marked ataxia, and the patient complained of weakness in the legs. The deep reflexes were depressed, this being more marked in the lower extremities.

Admission laboratory work was as follows: R.B.C., 4.52, W.B.C., 9,000, hemoglobin 13 gms.; urine was negative except for one plus sugar and a few granular casts and W.B.C. on microscopic. The sickle cell test, cutaneous tuberculin reaction, Schick test and blood Kahn test were all negative. Cerebrospinal fluid was clear, pressure 122 mm. of water, no cells, Pandy four plus, sugar 85, chloride 492-810, total protein 281 mg. per cent, respectively; culture remained sterile. Blood chemistry revealed total protein 6.5 gm. per cent, and non-protein nitrogen 32 mg. per cent. X-ray of wrists was negative for evidence of heavy metal poisoning.

After admission the patient became progressively weaker, and was unable to move both upper and lower extremities voluntarily. He was afebrile, anorexic, apathetic and perspired profusely. On the seventh hospital day, the muscular weakness was unchanged, but the patient appeared more alert and was less querulous. He was able to move his hands a little, but had a very weak grasp. No sensory changes could be elicited. He was painful, however, when manipulated in any manner. Head drop, nuchal and back rigidity, and foot-drop were noted. On the twelfth day, the patient could move the upper extremities, but could not pick up objects. On the

seventeenth hospital day, examination of the spinal fluid revealed no cells, but the protein content was 360 mg. per cent.

Therapy was mainly symptomatic and supportive at all times. He received 300,000 units of procaine penicillin, intramuscularly, daily for eleven days. Parenteral polyvitamin solution (Vi-syneral), 1 ampule, was given daily. Thiamin chloride, 5 mgm. daily, ascorbic acid 100 mgm. every other day, liver extract and soluble vitamin B complex (PolyB), intramuscularly, three times a week and glutamic acid (Glutamicol) 9 gm. daily, were used. Physiotherapy in the form of hydrotherapy, passive exercise, massage, and non-luminous heat to extremities was started on the fourteenth hospital day and continued until discharge.

Gradual improvement was noted in the patient. By May 8, 1950, he walked with some support and was able to use his arms and hands. By May 20, 1950, considerable return of power was noted in the lower limbs, and the child was able to walk alone but exhibited a wide base and some ataxia in his gait. The deep reflexes continued to be markedly depressed. Examination of the cerebrospinal fluid revealed 12 cells per cu. mm. and negative Pandy reaction. He was discharged on May 22, 1950. When last examined by one of us (R.B.S.) on November 13, 1951, the child was perfectly well.

On the basis of the initial complaint and findings, the diagnosis of measles encephalomyelitis was first entertained. However, in view of the clinical progress of the illness, the Guillain-Barré syndrome following measles became the logical explanation for the child's clinical picture which was characterized by ascending, symmetrical paralysis, marked motor weakness overshadowing negligible sensory changes; albuminocytologic dissociation in the spinal fluid, and gradual, but complete, recovery.

The Guillain-Barré syndrome was described in 1916 as a slowly progressing ascending paralysis of the body, starting in the lower extremities. A number of descriptive terms has been applied to the condition, such as acute infectious polyneuritis with facial diplegia, radiculoneuritis and Landry's ascending paralysis.

The etiology is obscure. A virus etiology has been postulated, but not proven.[2] The disease is known to occur after many infectious states, but it has also been found associated with non-infectious conditions. Regarding infectious etiology, it is known to

follow in the course of acute upper respiratory infections, pneumonia, measles,[3] mumps, scarlet fever, encephalitis, influenza, varicella, pyodermia, tuberculosis and syphilis. Recently, infectious hepatitis and infectious mononucleosis were reported as apparently precipitating illnesses.[4] Of the non-infectious conditions, it has been associated with serum sickness, sulfonamide intoxication, diabetes mellitus, artificial fever and metastatic carcinoma.

The pathology is not characteristic or consistent. Most workers describe degenerative changes involving the nerve roots and peripheral nerves and secondary degenerative alteration in the anterior horn cells.[2] Since most cases in childhood recover, there is a paucity of pathologic data available.

The clinical picture is diversified, but rather characteristic. The onset is usually preceded by some upper respiratory infection. After a latent period of several days or weeks, headaches, mild aching pains in back and legs are the usual prodromata. Fever is usually absent. The earliest neurological symptoms are referable to the sensory system and are usually manifested as numbness or paresthesia of the hands and feet. Shortly afterwards, the motor signs develop. They appear first as bilateral symmetrical weakness and later paralysis. Once motor signs develop, the sensory changes, which are mostly subjective, are overshadowed. The motor signs vary from slight weakness to complete quadriplegia, paralysis is characteristically ascending and symmetrical. Occasionally the respiratory muscles are involved. The deep reflexes are diminished or abolished, but the superficial reflexes are present. When the cranial nerves are involved, it is usually the seventh that is affected.

The cerebrospinal fluid presents the striking change of increased protein to a high level, but no increase in cells. The height of the protein content usually corresponds to the acme of the illness.

The prognosis is favorable in this condition, particularly in children. There have been adult mortality rates reported from 14-42 per cent. However, in children, deaths are rare, although they do occur.[4] Gradual recovery occurs over a period of weeks or months with complete recovery in four to six months.

The differential diagnosis includes poliomyelitis, lead poisoning, neuritis associated with avitaminosis, and diphtheritic neuritis. Sudden occurence of flaccid paralysis, sometimes with muscle tenderness and meningeal irritation, may suggest poliomyelitis. Clini-

cally, the afebrile course, symmetry of limb involvement rather than the spotty paralysis or confinement to single muscle bundles, and the occurence of subjective and objective sensory changes characterized the syndrome. Study of the cerebrospinal fluid will also aid in differentiation.

With lead poisoning and neuritis associated with avitaminosis, the history, clinical course, spinal fluid findings and response to vitamins, all help in clarifying the diagnosis. Postdiphtheritic neuritis may simulate the syndrome.[5] History, throat culture or culture of cutaneous lesions may reveal the diphtheria bacillus. In postdiphtheritic neuritis, the elevation of spinal fluid protein is quantitatively much less than that in the condition reported here.

There is no specific treatment for the disease. Therapy is symptomatic and supportive.

SUMMARY

1. A case of Guillain-Barré syndrome is reported.

2. This case presented the characteristics of onset of symptoms seven days after developing measles, progressive, ascending, symmetrical paralysis of extremities, albumino-cytologic dissociation of the spinal fluid, and complete recovery.

3. A general discussion of the etiology, clinical manifestations and differential diagnosis of the syndrome is given.

4. Although the prognosis is generally good, it is to be remembered that death may occur from respiratory paralysis.

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REST AND POLIOMYELITIS*

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In this study an attempt is made to outline the pathomechanism of poliomyelitis, departing from two sets of observations.

The recognition that bed rest is capable of arresting the progress of poliomyelitis in its preparalytic stage was proved by Russell.[1, 1a] His observations, in less definite form made already by Wickman,[2] have been confirmed by Hargreaves,[3] and by Horstman.[4] The method of treatment advanced by this author, termed "positional-nutritional method," and applied in the acute, subacute and chronic stages, served as the other set of observations. Maximum of rest is employed by keeping the patients in bed in head-down position for many months. Rest is complemented with high vitamin and liver diet, forced respiratory exercises, and a new form of physiotherapy, termed "pattern stimulation."[5, 5a] The partial revival of muscle function in the chronic cases, and its restoration in the acute and subacute cases, were accomplished in twenty-four cases altogether.

That an acute, contagious, inflammatory disease, already in progress, could be halted by simple bed rest seems to be a fundamental observation of the utmost importance.

The preparalytic stage of poliomyelitis is encephalitic in nature.[6, 7, 8, 1a] From this localization the virus is carried to the ganglionic cells of the bulbar region and of the spinal cord. The transmission is neither lymphatic, nor hematogenous, nor is it propagated by the spinal fluid. Apart from the fact that the virus had practically never been recovered from these media, the arrest of poliomyelitis in the preparalytic stage by bed rest alone is incompatible with the assumption of a circulatory transmission.

Since the continuation of physical activity during the preparalytic stage is followed by paralysis one to three days later, while bed rest prevents its development,[1a] it is proper to assume that the means of muscular stimulation and that of virus propagation are identical.

This leads to the first proposition. *It is the nervous stimulus which carries the virus to the ganglionic cells, to the nervous end plates, and possibly to the muscle proper.* Both, the skeletal

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muscles[9] and the heart muscle[10] show definite involvement, the former already during the first week of the disease, in the human as well as in the experimental animal.[9a]

Performances controlled or modified by the bulbar ganglia, such as eye movements, function of the facial muscles, of the tongue and of the vocal cords, deglutition and respiration, however, cannot be influenced by bed rest. In physical activity as in bed rest, the muscles effecting these functions are under constant central stimulation greatly increased during fever, restlessness, nausea and vomiting. So it happens that Horstman,[4] who confirmed the beneficial effects of bed rest in the spinal form of poliomyelitis, *saw no benefits from it in the bulbar form of the disease.*

What happens to the viral bodies which became arrested? They had been barred from further progress at the height of their virulence, judging from the cases which failed to observe bed rest and developed severe forms of paralysis a few days later. The virus was partly discharged, but some of it must have remained within the host in an apparently indifferent state. The fixation of the virus to the host cell seems to be rather intimate. Rous[11] and his co-workers, who demonstrated the resistance to separation of the host from the virus, state that: "In due course the disease is overcome, though the virus itself may persist in occult form in association with cells it does not kill." In the observations under discussion the poliomyelitis virus had been overcome by bed rest, leaving the positive neutralization test, almost universal in the human race, as the only indicator of its intimate contact with the body.[12] The arrest of the virus must be a regular occurrence in the human race. "Practically everyone, and frequently early in life, becomes infected with several viruses which we call poliomyelitis viruses, but the clinical syndrome called poliomyelitis is a rare manifestation, perhaps only a 'complication' of these infections" (Hammon[13]). The virus halted and associated with the host cell will persevere there until loosened up by some factor and then thrust upon the nervous pathways by physical activity generating stimuli of necessary strength and succession to carry them.

The second proposition states that the time when the virus first enters the organism, and the time when it becomes invasive are in no definite relationship. Theoretically, they may be separated by any interval. The main issue is not the entrance of the virus

but its separation from the host cell where it had established itself.

The discharge of waste material from the bulbar region occurs through the lymph vessels emptying into the nasopharynx.[14-17] During convulsions with tonic-clonic cramps and increased intrathoracic and intra-abdominal pressure, ink, injected into the subarachnoid space during experimental epileptic seizures in the dog, practically exudes from the nostrils. This occurs if there is a block set up between the cervical and thoraco-lumbar parts of the subarachnoid space.[16] The tonsils and the lymphoid apparatus of the nasopharynx form the exit to the lymphatics of the bulbar region. They allegedly also exert a "sucking effect" on the lymph vessels. These physiological considerations make the detrimental effect of tonsillectomy understandable, more pronounced in the bulbar form of poliomyelitis.[18] Tonsillectomy affects both the sucking mechanism and the exit of the lymphatics which ought to drain the bulbar region. If cases with acute and chronic inflammations of the nasopharynx would be included, the statistical evaluation of tonsillectomy with reference to poliomyelitis might look even more impressive. The blocking or narrowing of the exit of the lymphatics has serious consequences. The virus on its way out stagnates and multiplies within the lymphatics; physical activity, coughing, sneezing, fever, muscle tension and vomiting force it back towards the nervous system.[16, 17] *With the back flow of the lymph, the bulbar region becomes flooded with viral material and decomposed nervous tissue,* starting the second phase in the course of poliomyelitis, with paralysis in its wake.

The lymphatics which drain the thoracolumbar region empty into the intestines, eventually.[16] If an acute or chronic inflammatory process of the intestinal tract blocks or narrows the exit, stagnation, multiplication and back flow of the virus will occur. The virus re-enters the spinal cord, accounting for the paralytic phase of poliomyelitis.

It has been stated by several investigators that, "diarrhea, angina, and bronchitis may be accepted as consequent upon the elimination and not upon the invasion of the virus" (Wickman[2, 19]). If this be the case, the inflammation of the mucous membranes through which the virus has to leave the organism would find a simple explanation. Since the discharge of the virus may go on for a considerable length of time prior to the development of

poliomyelitis, as demonstrated in a number of well-observed cases,[19] inflammation of the site of exit with stagnation and back flow of the lymph containing the waste material will ensue, followed by re-entry of the causative agent into the nervous system.

The invasion of the ganglionic cells is not simultaneous with the onset of the paralysis. As Bodian[6a] states: "The cellular pathological reaction precedes the paralysis by at least one, and often several days." After the virus reaches the ganglionic cells, an inflammation sets in accompanied by severe edema, mostly of the gray matter, but the white matter is also not spared.[24] Since the degeneration of the ganglionic cells takes place mainly in the vicinity of the inflammatory reaction, further since the paralysis is not simultaneous with the invasion of the ganglionic cells, finally since the paralysis is invariably, even if only partly, reversible if the individual survives, hence connected with a time limited process, the paralysis can be regarded as the consequence of a circulatory disturbance affecting already damaged ganglionic cells.

The circulatory disturbance, if compared with similar pathological findings following Stenson's ligature of the aorta[20], resembles an ischemic process.[21] Both are characterized by degeneration of the ganglionic cells of the anterior horn with little or no involvement of the posterior horn and of the posterior fasciculi, by degeneration of the gray matter with little involvement of the white matter, and finally by flexion contractures of the joints followed by fibrous fixation. Nelson[22] and also Smith[23] and co-workers assumed that ischemia in poliomyelitis is caused by the involvement of the autonomous nervous system. In this author's opinion, the circulatory disturbance starts with congestion of the veins in the spinal cord and in the vertebral canal. The congested veins mechanically affect the arteries shortly before they enter the cord through the intervertebral foramina. Thus the arterial inflow is reduced. But something else may also happen. Compression of circumscribed arterial segments may lead to reflex ischemia in the main segments of the artery as observed in trauma. All this would account for the composite pathological picture of venous congestion combined with reduced arterial inflow. A pathology ensues resembling Volkmann's ischemic contracture with which poliomyelitis has more than one trait in common. The passive hyperemia leads to the atrophy of the vertebrae observed almost invariably already dur-

ing the first weeks of the disease regardless of the muscular involvement. A condition termed "paralytic spine" follows which may disappear either spontaneously or in the course of the positional-nutritional treatment.[5c, 5d] The beneficial effect of constant bed rest in head-down position on both the paralysis and the paralytic spine can be explained by the emptying of the congested veins, draining of the edema, and the consequent release of the ischemia.

The head-down position, termed "fundamental position of rest of the spine" (Farkas[5b]) has been employed successfully in both sciatica and osteoporosis of the spine in which, in the author's opinion, the venous congestion plays an important part.[5b, 5c]

The third proposition states that the paralysis is of ischemic nature; it affects the ganglionic cells already altered by virus invasion.

The inflammatory reaction is, as a rule, of such a vehement nature that it is wholly out of proportion to the degenerative process in the ganglionic cells.[2, 24] The vascular and perivascular spaces are filled, almost to bursting. Moreover, the inflammatory reaction is not limited either to the region of degenerating cells or to the spinal cord. Major portions of the lymphatic and reticuloendothelial systems are involved. The lungs, the spleen, the intestinal wall and the liver are markedly hyperemic; the Peyer patches and the thymus are enlarged. The liver, the spleen and the adrenal medulla show foci of necrosis.[24, 25] Areas of hemorrhages within the spinal cord as well as in other organs, such as the adrenal medulla, have also been reported. There is an extreme degree of edema in the cord, mostly in the gray matter, but the white matter is also not spared. Eosinophilic cells appear within the ganglionic cells.[6, 20, 20a, 27] A number of investigators report marked leukopenia* during the febrile period.[26, 2] *This is a violent systemic inflammatory reaction.* The lymphoid involvement is of such intensity that Burrows[29] proposed the term "acute lymphatic hyperplasia" for poliomyelitis. All in all, it appears that *this is an allergic reaction with the spinal cord as the shock organ.* Many of the fatal cases develop in a true anaphylactic manner. In others arthritic phenomena prevail, involving one or a great number of joints.[30] It seems to be probable that the severe pain, the

*The stage of leukopenia is apparently of short duration or may be even missing because muscular activity (as in restlessness, cramps, nausea, vomiting), and psychic excitation are accompanied by leukocytosis[67]).

rigidity of the spine, and the stiff neck, relieved in the prone position, are partly caused by the involvement of the apophyseal joints, emerging and disappearing in a true hyperergic fashion. The inflammatory reaction does not spare even the muscles showing "edematous swelling, hyaline degeneration besides extreme passive hyperemia in the capillaries." (Carey[9, 96])

Pain in poliomyelitis during the preparalytic stage resembles that in any fever. The more localized severe pain is partly due to the congestive allergic state of the muscles accompanied by local ischemia, partly to the allergic state of the joints, particularly of those of the spine harboring the shock organ. As allergic conditions may develop gradually with the ebbs and tides in the congestive-edematous states, so fluctuates the pain. Even the paralysis frequently shows fluctuations until it either recedes or becomes a full fledged affair.

Allergic reactions in the central nervous system have been described by several investigators.[21-35] The familial periodic paralysis following ingestion of large amounts of carbohydrates may belong to this variety, with emphasis on potassium exhaustion as a corollary.[36, 37] Its familial appearance, its sudden emergence following carbohydrate ingestion, and its disappearance after a short duration raise the possibility of its allergic (atopic) nature.[56] Investigating the cause of encephalitis following vaccination against rabies and smallpox, and accompanying measles, Rivers and Schwenker[34] injected small doses of brain tissue into monkeys for several months, and succeeded in producing allergic encephalomyelitis. Freund[41] by injecting an emulsion of brain and killed mycobacteria into guinea pigs, brought about encephalomyelitis in a short time. Morgan[39] used brain and killed tubercle bacilli emulsion successfully. Ferraro,[40, 40a] and co-workers employed Freund's technique and brought about also chronic allergic encephalomyelitis in monkeys in a relatively short time. The inflammatory changes they encountered in the nervous system appear to be similar to those seen in poliomyelitis.

They proved their point also in preventing the development of allergic encephalomyelitis by desensitization carried out for a long period preceding inoculation.[40b]

The fourth proposition states that the systemic inflammatory reaction in poliomyelitis is apparently of allergic nature with the spinal

cord as the shock organ. It is assumed that the virus acts as a sensitizing agent as well as an antigen from the time it entered the organism. During the period in which no virus activity is manifested the sensitizing process is probably very slow. From the moment of the separation of the virus from the host cell the sensitizing properties of the virus gain momentum. *The main factor remains the release of the virus from the host cell.* Rous[11] states that the virus is immediately released when the host cell succumbs, hence the degree of vitality of the host cell plays an important part in the process of separation. Thus such release may occur more easily in the early years of life when the nervous system is not yet fully developed.[65]

If the process of sensitization is gradual, if it is protracted, if no brutal external intervention occurs, complete desentization with immunity will follow. If, however, during the process either the amount and virulence of the virus increases by release of viral material from less stable or even destroyed cells, while the activity propagating the virus suddenly greatly increases, or the site of excretion of the virus becomes occluded, allergic or even anaphylactic reactions may ensue.

Lesser-greater degrees of invasion of the nervous system may occur unnoticed several times during life. The pathological findings of old cases show frequently foci of more recent inflammation. This mechanism may also account for the observation that the paralysis develops not rarely in stages, sometimes requiring even weeks. According to a recent report of Sédallian and Gaillard[84] over 5 per cent of the cases show the development of paralysis in two stages, requiring 8-30 days.

In one of the most thorough papers on poliomyelitis of the previral era, Brackett[49] distinguishes between endemic (sporadic) and epidemic poliomyelitis. It appears that the endemic cases do not tend to instigate an epidemic except for definite environmental circumstances (see below), and they seem to have less respect for the "only predisposing factor: age." In the well-known tragic occurrence of five cases of poliomyelitis in one family following tonsillectomy,[45] in spite of the contact between the sick children and many healthy ones, no epidemic followed. Not even the non-tonsillectomized, two-year-old member of the same family became ill although it discharged poliomyelitis virus in its stools. In

another instance, reported by Leake,[44] vaccination with treated poliomyelitis virus caused poliomyelitis in twelve children with five fatalities, but without an ensuing epidemic.

According to this concept, the virus of poliomyelitis has been present in the organism prior to both the tonsillectomy and vaccination, so in both instances the intervention was the factor of revitalization of the virus. In this connection, another proved instance of endemic poliomyelitis should be analyzed. The case of Brown, Francis, and Pearson[45] harbored virus of poliomyelitis in his stools for nineteen days without any signs of the disease. On the nineteenth day, the patient participated in a strenuous canoe race, using his arms as paddles, and this was followed by arm paralysis. The virus had been separated from its host cell at least nineteen days prior to the disease. It entered the spinal ganglia and was discharged into the intestinal tract through the lymphatics. Excretion of viral bodies combined with decomposed nervous tissue went on for at least nineteen days. Suddenly extreme physical activity carried great quantities of viral bodies to the ganglionic cells. The spinal cord, already sensitized, reacted with paralysis. The latter developed gradually within a week. Apparently, the allergic reaction alone would not account for the paralysis despite congestion and edema of the cord. Not until the ischemia set in, which may take some time to develop, did the paralysis become definite. The other factor worth noting is the long interval between the appearance of the virus in the feces and the paralysis. As mentioned above, the discharge of waste containing the virus may account for the inflammation of the mucous membranes through which the excretion takes place. This inflammation may represent an obstacle causing stagnation and back flow of the waste material.[46]

Possibly, the most important factor in the endemic (sporadic) form of poliomyelitis is that the virus, termed the "native strain," mostly an old dweller of the organism, increases its sensitizing properties after its separation from the host cell. Revived and multiplied, it combines with the decomposed nervous elements, then it becomes discharged until an obstacle is erected at the site of its exit. Then stagnation and back flow occur, the virus reenters the spinal cord or the brain stem, and paralysis follows. The main point is that in the endemic cases the virus causing

poliomyelitis is the very one which entered the organism, frequently, a long time before the first manifestation of its presence. Such a virus, if discharged and ingested by the environment, is harmless to them because their organism is immune to the native strain which they themselves harbor, except for unusual circumstances as exemplified in three different types cases of endemic (sporadic) poliomyelitis.

In the five children who contracted poliomyelitis after tonsillectomy, the surgical intervention might have played a twofold role, i.e., that of extreme nervous activity within the ganglionic cells controlling the pharyngeal region, and that of the factor separating the virus from its host. Through the intervention enormous amounts of stimuli were generated and carried the virus to the next relay station. The virus combined with degenerated nervous tissue could but partly be excreted because the site of exit in the pharyngeal region had been blocked by the surgical intervention just performed. Stagnation and multiplication of the virus followed with its re-entry into the bulbar region.

However, the virus might have been separated from the host cell prior to the intervention. The fact that, also the sixth two-year-old child excreted virus in its stools corroborates this assumption, except if one assumes that it ingested viral bodies excreted by the sick members of the family. Then why did it fail to develop the disease, especially at an age most susceptible to it? Because it was not operated on or because it had more protection from the disease than the rest? The proved role of tonsillectomy speaks for the former possibility. It is not quite impossible that in some children, perhaps in some families, as is the case with the Theiler virus of poliomyelitis in mice, the virus of poliomyelitis becomes periodically detached from its host, travels along the nervous pathways and becomes discharged usually without causing symptoms.[17] If this was the case with the tonsillectomized members of one family, it had been a revealing coincidence worth consideration.

Leake's experience gives us a clue for the mechanism of the separation of virus from the host. It also forms the transition from the endemic to the epidemic form of poliomyelitis. Two injections of treated poliomyelitis virus were administered in 6-8 day intervals. Pre-paralytic symptoms developed followed by paralysis several days later. "In every case in which the sequence

is known . . . paralysis began either in the same limb or in the contralateral limb in which the injection was made," (Leake[41]), an observation frequently made by the investigators.[1a]

The material incorporated was treated virus, i.e., virus deprived of its pathogenic properties. Two injections were needed to elicit the disease which followed 1-7 days after the second injection. The vaccine served as an allergen-antigen of unknown relationship to the virus of poliomyelitis already in the organism. It is hardly probable that the two were of identical strain. Most likely the vaccine was derived from a heterologous strain. The first injection separated and mobilized the virus already in the organism, and brought about sensitization. The second injection brought about the allergen-(antigen) antibody reaction with the paralysis in its wake. Although twelve children were stricken with paralysis, no epidemic followed. The explanation, as offered in the foregoing discussion, is that the virus discharged, although unquestionably ingested by the environment, was of the "native" variety for which the environment possessed immunity efficient enough under normal circumstances of life.

The fifth proposition states that in the endemic (sporadic) form of poliomyelitis the native variety of poliomyelitis virus, following its mobilization by factors other than virulent non-native (foreign) strains, acquires virulence, induces sensitization, and enters an antigen (allergen) antibody reaction.

From this the sixth proposition follows:
In the epidemic form of poliomyelitis virulent viruses of at least two different strains combine within the human organism. They are excreted by individuals or groups of individuals originating from different geographical locations.

Seddon[49] and his co-workers published an admirable report on the 1942-43 epidemic in Malta. It demonstrates one probable course of an epidemic. Malta is one of the most densely populated islands in Europe which underwent a relentless aerial bombardment from June 1940 to the end of 1942. Poliomyelitis has been sporadic, with no epidemic, since 1902. In 1941 and 1942 not one case of poliomyelitis had been reported until the middle of November 1942, when the epidemic started involving 486 cases out of which 57 were service men; among the native population 82 per cent were children under the age of five, and only four were above the age of twenty.

The overcrowding became more and more severe as the bombardment went on.

In a confused situation the analysis of a common occurrence in an unusual setting is one of the methods of distinguishing the relevant factors from the irrelevant ones.

The unusual factors in this epidemic were that it was a winter epidemic, that it occurred in a densely populated area, and that such a large number of adults, almost all of them strangers were involved. The overcrowding lasted for over two years without one single case of poliomyelitis. By November 1942, the food situation became almost desperate. Then adequate food supplies arrived. "It was at this time, in the middle of November, that the poliomyelitis epidemic started" (Seddon). The first cases occurred in the civilian population, followed two weeks later by cases among service men. Milk was very scanty until November. Full cream milk distributed in September and October 1942 amounted to 14 tons; in November and December it jumped to 55 and 59 tons, respectively. 397 children, under five, were affected; the number of those below three, presumably living largely on milk and milk products, amounted to roughly 300. Hence, the connection of the sudden outbreak with the sudden plentiful milk supply after a long period of want is justified.

The concept advanced requires a factor loosening the attachment of the virus from the host. Several such factors have been suspected by this author and many more will be found by others. Such factors may be mechanical, such as surgery or heat; biochemical as vitamin deficiencies[63]; biological as inoculations; preventive or therapeutic.[50-52] Price[53] mentions that in Africa, "injection paralysis" not infrequently follows injection or vaccination in little children. Epidemics, such as measles, mumps, influenza and dysentery, not rarely, precede or accompany poliomyelitis epidemics.[13] In the Maltese epidemic, typhoid fever had been rampant prior to and during the poliomyelitis epidemic; also 120 cases of ulcerative colitis were reported with complete recovery following vitamin B administration. Their role in the precipitation of poliomyelitis is probably twofold; they may bring about the loosening of the virus from the host cell as well as set up a barrière at the exit of the virus. Apparently everything which leads to a local edematous state of the host cell may instigate the revival of virulence. Dilution of virus plus immune serum reactivates

the virus. "This phenomenon can be demonstrated with a number of viruses including . . . poliomyelitis" (Andrewes[54]). Milk as the source of poliomyelitis epidemics appears frequently in the literature as a view advanced by authors known for the accuracy of their observations.[2, 55] In the Maltese epidemic plenty of milk was supplied after a long period of want. Undigested molecules of protein easily flooded the organism. They played the role of the heterologous proteinic substance injected by Leake. The revitalized, multiplying virus reached the ganglionic cells. Decomposed nervous tissue combined with the virus emptied into the nasopharynx, and into the intestinal tract, except when the exit was or became blocked or narrowed. The latter might have been caused by a preceding inflammatory (typhoid fever, ulcerative colitis), or allergic condition of the mucous membrances following sudden ingestion of large amounts of food, notably milk after a long period of want; or it followed the prolonged discharge of the virus prior to the onset of poliomyelitis. In consequence, virus stagnation in the lymphatics took place and the waste material re-entered the nervous system. A number of sporadic cases occurred with the excretion of virus material of the native variety. No epidemic might have followed if the native virus had not found its way into the organism of the service men.

As the stimulus carries the virus in the motor system from ganglionic cell to ganglionic cell, so seems the impulse to propagate the virus from the exterior to the interior of the body.

The most probable sites of entrance are the taste buds, representing at the anterior part of the tongue the facial nerve (chorda tympani), at the posterior portion the glossopharyngeal nerve, and at the epiglottis, the vagal nerve. As to the olfactory nerve, its receptors are embedded in the small mucous patch of a blind pocket in the narrow cleft of the upper most compartment of the nose.[57] Food particles could hardly reach the olfactory receptors under normal circumstances. However, during vomiting or too hasty swallowing, they might enter the olfactory nerve endings. Though the nasopharynx and the intestinal tract serve mainly as exits for the virus, they may also serve as portals of entry, as may the buccal and gastric mucosa, and probably also the cornea. That the skin can offer entrance to the virus has been demonstrated by Leake. The virus travels along or between the nerve fibrils[58] of the sensory and autonomous nervous system, reaches the ganglionic

cells and is transmitted to the motor ganglionic cells coupled with them. Hence, the paralysis will affect preferably the region whose sensory endings picked up the virus.

In the Maltese epidemic the native strain of virus was separated and discharged in a number of natives following ingestion of milk. The revitalized virus was excreted and ingested by the service men. In their organism it entered into a combination with the "foreign strain" of virus of the service men. The combination of the two brought about the inflammatory reaction followed by paralysis. Now the service men excreted their own revitalized virus, which was ingested in turn by the natives, leading, by combination of the two viruses, to a severe allergic reaction in them. A vicious circle was set up by exchange and combination of two varieties of viral bodies.

Experimental evidence of such mechanism was presented by Howe and Bodian.[39] They inoculated two monkeys with one strain of poliomyelitis. After two months one of the monkeys was inoculated with a heterologous strain. This led to a fulminant form of poliomyelitis with 107° F., with utter prostration of the animal. Both monkeys were sacrificed. The doubly inoculated animal showed a most severe form of degeneration and inflammation in the olfactory bulb, while the control had insignificant changes only. In this author's opinion, this experiment was closest to the human disease.

Seddon assumed that the Maltese epidemic was a consequence of the fact, "that this minority had come into contact with a virus that was new to them and to which they were susceptible." However, the contact alone was insufficient since such contact lasted for over two years without leading to the outbreak.

Seddon mentions that the wealthy families were practically spared during the epidemic. If by wealthy families more adequate food and less crowding are meant during the hard times for the rest, their being spared is understandable, if the author's reasoning is correct. First, they had not been in the state of utter want, thus the arrival of adequate food supplies did not represent a sudden change in their nutrition. Second, they had less opportunity to enter into virus exchange with strangers since they did not live together with them in crowded quarters.

Poliomyelitis prevails in countries with large numbers of newcomers mixing with the native population, such as countries with

large numbers of immigrants. The overcrowding facilitates the exchange and combination of different strains. Such was the case in Amsterdam, where, in 1943, following the expulsion and crowding of the Jewish population, 608 cases were seen, while from 1924 to 1947 poliomyelitis has been sporadic only with 1-54 cases yearly.[60] Something similar happened in Israel in 1949 and 1950 following the mass immigration.[66] In Berlin, the post-war outbreak had been preceded by mixing of large masses of people coming from distant countries, all just recovering from the hunger years of the war. The outbreak in sparsely populated rural areas represents a special instance of mixing between parts of the population hailing from distant localities. They meet during the summer months, when also the heat may have an important bearing on the hyperergic state. The winter is the season of scarce food supplies in the rural areas followed by the plenty of the summer months. Thus, both factors, the mixing of people from distant places and the sudden relative plenty of foodstuffs, are encountered. In city areas the population lives in crowded quarters all through the year. There the wealthier classes move to distant resorts during the summer months. It is among them that "the healthiest children," "the cream of the crop," are to be found. They have been frequent victims of poliomyelitis to the great astonishment of the investigators since the time of Underwood.[61]

Both sets of observations, from which this article took its departure, required more than simple presentation.

"Any experiment should be regarded with the greatest caution until it is confirmed by theory." (Sir James Jeans[62]). In this study such a theory has been advanced. It might bring us a good step closer to the clarification of the poliomyelitis problem. *Et estimatio quoque causae saepe morbum solvit.*

COMMENT

(1). The question whether the virus be an organism (Andrewes), a molecule (Stanley), or a particle within the cytoplasm (Bawden), discussed at the Second International Poliomyelitis Congress, Copenhagen, 1951, loses its practical significance by the assumption that the attack of polioymelitis is chiefly of allergic nature.

(2). The epidemiological character of poliomyelitis, which makes halt at some definite lines of demarcation, finds its explanation in the requirement of thorough mixture of people originating

from distant geographical locations while in the state of discharge of virulent viral bodies.

(3). The main factor preceding poliomyelitis is the sensitization of the organism by the mobilized native strain. Among the factors of virus mobilization, vaccination, curative injections and surgery have been mentioned. These factors may account for the observation of Horstman[46] and others that among the American soldiers sent to the Pacific ten times as many cases of poliomyelitis occurred than among those from which they were selected in the United States. Prior to their embarkation the soldiers have been, as a rule, vaccinated against a number of diseases. The change of the climate and of nutrition, the physical and psychical strain preceding their departure, added their share to the outbreak. But also another factor has to be mentioned. The troops arriving at their destination have been mixed into new units with those coming from other parts of the world, and with those already in the Pacific; common living quarters had to be established, thus a number of conditions preparatory to the epidemic have been created.

(4). The native strain as an allergen can be postulated whenever sensitization instead of immunization takes place. This would be even more in accordance with the nature of allergic phenomena. The observation, however, that endemic cases regularly occur without ensuing epidemics, as has been the case in Malta for forty years, speaks against this assumption. Only when different virulent strains mix within the organism, to be discharged and incorporated again, does the epidemic start. The attack of poliomyelitis by the native strain requires its re-entering the nervous system combined with decomposed nervous tissue. The mechanism of epidemic poliomyelitis is similar insofar as the incorporation of viral bodies alone probably never occurs, they necessarily are combined with decomposed nervous elements. The role of the latter may be paramount.

(5). In Malta, 57 servicemen fell victims of the disease, among them only 4 were Maltese, while over 400 native children have been afflicted. This demonstrates two things. First, the virus discharged by adults has less infective property for adults than for children. Secondly, virus discharged by children has more infective property even for adults than that discharged by grown-ups. Otherwise the number of Maltese servicemen would have

been not so negligible as compared with the number of non-native servicemen afflicted. The former have been practically spared apparently because the virus discharged by the native children, although highly infective, had but little effect on them since they have been immune to this strain of virus. On the other hand, virus discharged by (non-Maltese) adults proved to be less effective for grown-up persons, as mentioned.

(6). Higher health standards seem to be more responsible for the rapid increase of poliomyelitis than high living standards. The loosening up of the virus in cells of decreased vitality or in the state of instability could be better understood by the former. High health standards mean, among others, regular vaccinations, large scale tonsillectomies, frequent injection therapy. But something else should also be pointed out, which may play an important role in the decreased vitality of the nervous elements. First, it is the birth trauma caused by too generous use of the forceps. Secondly, it is the poisonous effect of anesthesia, so indiscriminately applied at the last phase of labor, almost since the advent of general anesthetics.

(7). The fact that the antibodies to the P virus may be transmitted through the placenta to the fetus probably accounts for the occurrence of P in infants even during the first months of life. If such antibodies meet their specific antigens in a virulent stage, incorporated by the infant, an allergic reaction may follow. The number of such cases amounted to roughly five per cent in the more recent epidemics.[26]

SUMMARY

The study is based on two sets of observations. The first showed that bed rest during the preparalytic stage arrests the disease, except for the bulbar form. The second demonstrated, in a limited number of cases, that by the help of constant bed rest in the head-down position revival of muscle function can be achieved even two-three years after the onset.

The role of the nasopharynx and of the intestinal tract is emphasized as the sites of excretion of the lymphatics from the brain stem and from the spinal cord. If the sites of discharge are destroyed, as after tonsillectomy, or blocked or narrowed as during inflammatory states, stagnation and back flow of the viral bodies may occur. The waste material thus may re-enter the nervous system accounting for the paralytic phase of the disease.

The following propositions are suggested:

1. It is the physiological stimulus which carries the virus from its encephalitic localization to the ganglionic cells of the bulbar region and of the spinal cord, from there to the end plates and to the muscle proper.

2. The time when the virus enters the organism first and the time when it becomes invasive bear no definite relationship to each other. They may be separated by any interval. The main issue is not the entrance of the virus but rather its separation from the host cell where it has established itself.

3. Muscle paralysis is brought about by combined ischemic (arterial) and congestive (venous) conditions in the spinal cord, affecting the ganglionic cells already altered by virus invasion.

4. The inflammatory reaction is a systemic response of the organism, it apparently is of an allergic nature with the spinal cord and brain stem as the shock organs. All allergic reactions require: first, that the virus (combined with decomposed nervous tissue) should also act as a sensitizing factor. Another requirement is that there be a second invasion of the body by homologous or heterologous antigens-allergens to start the allergic or anaphylactic phenomena.

5. In endemic (sporadic) poliomyelitis the virus, within the organism for a variable length of time, and termed "native strain," enters the antigen (allergen)-antibody combination after having been separated from the host cell by factors other than non-native (foreign) strains of poliomyelitis virus.

6. In epidemic poliomyelitis the combination (union) of virulent viruses of at least two different strains, within the organism, is required. The different strains are excreted by individuals or groups of individuals originating from distant geographical locations.

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THE VALUE OF BONE MARROW STUDIES IN NEUROBLASTOMA*

Report of Case

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Malignant tumors originating in the adrenal medulla or the sympathetic nervous system are uncommon, occurring predominantly in infancy and early childhood. The early clinical diagnosis of tumors of the neuroblastoma group is indeed a difficult one. Bone marrow studies may, under circumstances, be the only diagnostic method available, as metastases to bone may occur at an extremely early stage of the disease.[1] In 1938, Kato and Wachter[2] and, independently, Albertini and Willi[3] first reported the presence of characteristic tumor cells in bone marrow smears. Since then three additional reports on the subject have appeared in the literature.[4, 5, 6]

We are presenting the following case of neuroblastoma, illustrating interesting hematological features and the use of bone marrow smears for the diagnosis of the neoplasm.

CASE REPORT

G. G., a 3½-year-old white boy of Italian extraction, was first admitted to Kings County Hospital on June 23, 1949. About 2½ months prior to admission the mother first noticed a black discoloration of the left upper eyelid. There was no history of trauma. Two weeks later the left lower lid became similarly discolored. This was followed by darkening of the right lids. The darkening of the lids was accompanied by protrusion of the eyes. Anorexia, pallor, fatigue and irritability followed. Head enlargement with prominent veins appeared two months prior to admission. The child also began to lose hair. Weight loss (amount not known) was noted at that time. An increased tendency to bruise was also noted. The diagnosis of Cooley's anemia was made three weeks prior to admission at another hospital, and the child received two

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transfusions, one, three weeks, and another, one day prior to admission. The transfer to the Kings County Hospital followed. On admission the temperature was 99.6° F.; pulse 102, respirations 20, blood pressure 90/60. Significant findings included proptosis of both eyes, the left more than the right. The head appeared enlarged, the circumference being 52 cm. The eyelids were pigmented dark brown-purple. There was a diffuse, hard swelling of the parietal area and a smaller swelling of the left aspect of the forehead.

Moderate sized lymph nodes were palpable in the axillae, inguinal and left postoccipital areas. Anterior and posterior cervical lymph nodes were slightly enlarged and not tender. The fundi were poorly visualized. Throat and tonsils were injected and red. Heart and lungs were normal. The edge of the liver was palpable 2½ finger-breadths beneath the right costal margin. The lower pole of the spleen was firm and palpable 6.5 cm. beneath the costal margin. The tentative diagnosis on admission was chloroma. X-ray survey of the skeleton revealed the following: Enlargement of dimensions of the skull with extensive dehiscence of sutures. Localized coarseness of bony architecture and evidence of sun ray striated area of density in the frontal region of the cranium. Superior and medial confines of left orbit had lost their usual definition. Examination of pelvis and both femoral and upper extremities revealed alteration in consistency and patchy areas of sclerosis and irregular decalcification. Feet, knees, tibia and fibula,—no changes were noted. The x-ray findings were considered as compatible with an underlying blood dyscrasia. On June 28 an examination of eye grounds disclosed marked papilledema of the left eye and a blurring of the nasal part of the right disc. There were no hemorrhages. The patient was discharged to the clinic on June 29, 1949.

A short readmission for transfusion followed on July 11, 1949. Clinical findings were essentially the same.

The child was readmitted for the third and last time on July 16, 1949, because of severe abdominal pain, delirium and occasional loss of vision. The child appeared gravely ill with grossly distorted facies. The head was markedly enlarged. The veins were dilated. The left eyelid was filled by a hematoma. Both eyes were proptotic with amaurosis of the right eye and absent pupil-

lary reflexes on both sides. The discs showed severe edema and marked venous engorgement; no retinal infiltration was noted. The pharynx was moderately injected. Right drum was bulging, dark bluish in color, probably because of retrotympanic hemorrhage. There were a few enlarged matted nodes over the otherwise supple neck. Lungs were clear to auscultation and percussion. The heart was enlarged to the left and protodiastolic gallop was heard over the apex. There was a blowing systolic aortic murmur. The liver edge was palpable 4 finger breadths beneath the right costal margin. Many stony hard masses were felt throughout the abdomen. The abdomen was not tender. In spite of therapy with Aminopterin,® 2 mgm. for three days, and multiple blood transfusions, the child expired on July 29, 1949.

TABLE 1. *Peripheral Blood Counts.*

	5-26-49†	5-29-49†*	6-1-49†	6-22-49†*	6-30-49	7-11-49*
Hemoglobin	8 Gm	10.2 Gm	10.3 Gm	10.3 Gm	10.5 Gm	....
R. B. C.	**2.6 mil	3.48 mil	3.58 mil	2.68 mil	....	....
W. B. C.	4,950	6,350	8,300	6,150	5,100	6,300
Polys Neutrophiles	43%	60%	67%	39%	40%	61%
Juveniles	2%	....	3%	....	8%	....
Myelocytes	....	....	....	9%	4%	....
Metamyelocytes	....	....	....	....	2%	....
Promyelocytes	....	....	....	....	1%	....
Blasts	....	....	....	....	1%	....
Polys Eosinophiles	....	....	....	....	2%	....
Polys Basophiles	....	....	....	....	1%	....
Immature Lymphocytes	....	....	....	....	....	16%
Lymphocytes	52%	40%	29%	49%	41%	20%
Monocytes	3%	....	1%	2%	....	3%
Platelets	160,000	....	....	....	....	....

*Count following transfusion.
**Anisocytosis, poikilocytosis and an occasional target cell were constantly observed.
†Blood counts by courtesy of the Unity Hospital in Brooklyn.

During the stay at Kings County Hospital the Mantoux reaction 1 : 10,000 was negative. The urine was normal. The hematological findings are presented in Table 1. Bone marrow smears on June 27, 1949 revealed polys 15 per cent, bands 9 per cent, metamyelocytes 5 per cent, myelocytes 1 per cent, eosinophiles 1 per cent, lymphocytes 9 per cent, normoblasts 34 per cent and 26 per cent of cells which originally were called "blasts."

The autopsy (No. 24457) was performed seven hours after death. A striking deformity of the head was noted, corresponding to the clinical description. There was severe proptosis of the eyes, left more than right. Marked discoloration of lids was noted. The calvarium was covered with soft tumor masses, violet in color,

which could be cut with ease with a knife. The cranial sutures were also filled with similar tumor tissue to the extent that the bones of the calvarium fell apart after removal. The thickness of the bones was markedly increased, up to 3 cm. in the left temporal area. There, spicules of bone, embedded in tumor tissue, were externally overlying the bony plate, and radiating away from it. After removal of the brain, subdural and intradural tumor masses were found, penetrating into both orbital pyramids. The brain was compressed and destroyed by tumor tissue over the posterior

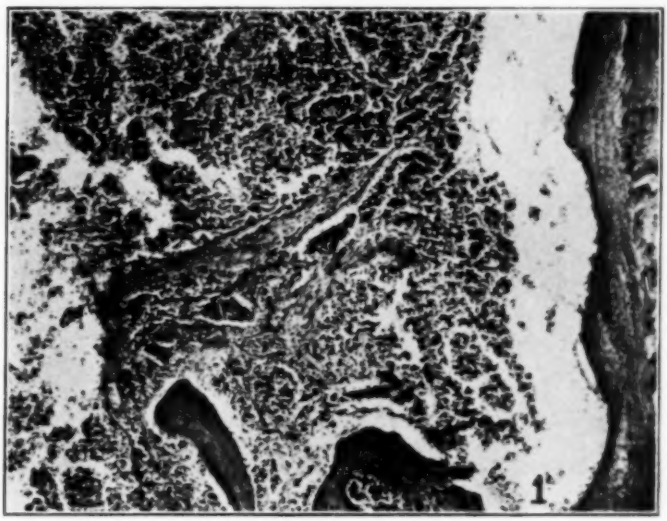

Fig. 1. Section of bone showing massive invasion of bone marrow by tumor with formation of pseudorosettes. Hematoxylin and eosine, X 55.

surface of the parietal lobe, and the tip of the left temporal lobe. Subarachnoid hemorrhages were noted. On section the ventricular system was slightly compressed but patent. The cerebellum and brain stem appeared normal. The eyes were examined and appeared normal on the external examination.

In addition, the autopsy disclosed presence of a large, nodular, retroperitoneal tumor mass, measuring 10 x 10 x 6 cm. and weighing 200 gm. This mass was located in the upper part of the

retroperitoneal space, around the pancreas, abdominal aorta and inferior vena cava. On section the tumor was for the most part necrotic and hemorrhagic. Its intact portions were soft and white-gray in color. Both adrenals could be isolated although they were partially embedded in the tumor. The weight of the liver was 1,010 gm. The organ was studded with white and soft metastatic tumor nodules measuring from 1 to 6 mm. in diameter. The preauricular, maxillary, cervical, anterior mediastinal, paraaortic,

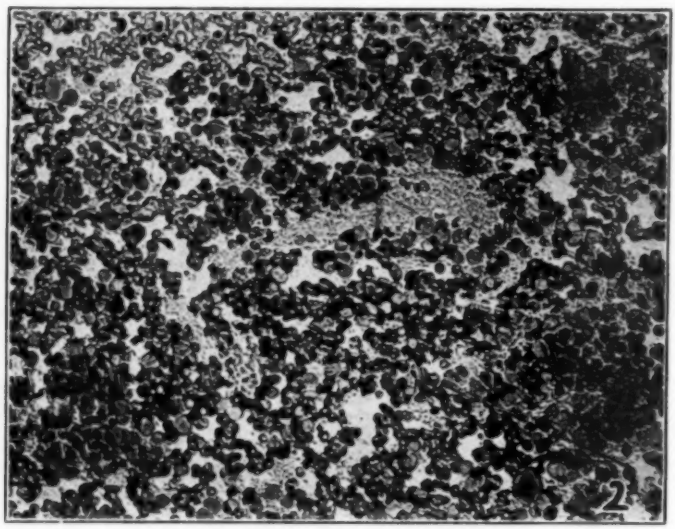

Fig. 2. Ante-mortem bone marrow smear showing infiltration by tumor cells, frequently in clumps. Cellular arrangement in the central portion of the picture is suggestive of a pseudorosette. Wright's stain, X 220.

mesenteric and inguinal lymph nodes were involved by the tumor. The lymphoid tissue of the intestine appeared hyperplastic. The lungs, heart, spleen, and kidneys were not remarkable on gross examination.

Microscopic examination revealed a tumor consisting of clumps of small, round, dark cells, about twice the size of lymphocytes, with a dark, prominent nucleus and a very narrow rim of protoplasm. Numerous pseudorosettes with a central core of pink homogenous material were observed.

In addition to the organs mentioned above the tumor also invaded the myocardium, both adrenals and all the bones available for section. In the marrow spaces frequent pseudorosettes were found (Fig. 1). Bielschowsky's silver stain failed to reveal neurofibrils within the tumor. The final anatomical diagnosis was neuroblastoma with multiple metastases. As there was no definite evidence that the tumor originated in either adrenal gland it was

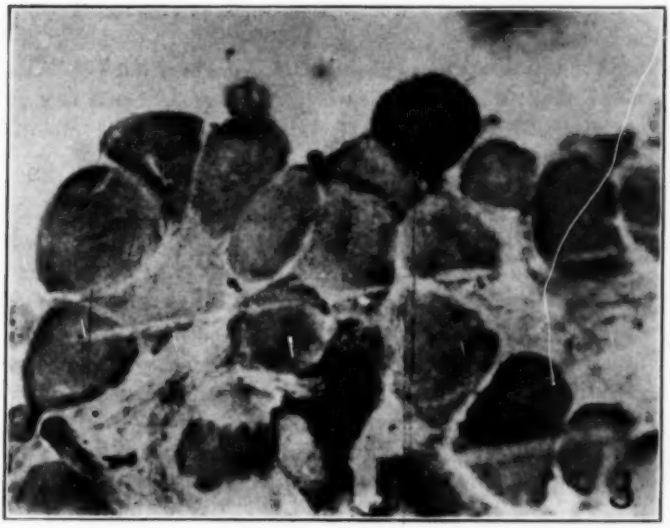

Fig. 3. Ante-mortem bone marrow smear showing clump of tumor cells arranged into mosaic pattern. Note very scanty rim of protoplasm surrounding the homogenous nuclei. Some immature bone marrow elements can be recognized in the photograph. Wright's stain, X 1100.

assumed that it originated from the sympathetic nervous system in the retroperitoneal space.

Once the post-mortem diagnosis was known, the bone marrow smears were reexamined. It was noted that the bone marrow was invaded by large mononuclear cells, which appeared singly and in sheets (Fig. 2). The sheets or conglomerates of cells were particularly well seen at the periphery of the smear. Individual cells in the clumps were pressed into a mosaic where each border fitted

snugly into the borders of the surrounding cells (Fig. 3). The size of the cells varied, but averaged 15 mu. At no time were there true syncytial formations noted, although occasionally the cell borders were partially effaced. The nucleus of each individual cell was large, with a finely reticulated chromatin net, and of pale-purple appearance as seen in Wright's stain. The nuclei were round or oval in cells which were lying freely, but polygonal within the aggregates of cells. Rare single nucleoli were noted in some nuclei. No coarse chromatin granules were noted anywhere. The cytoplasm formed a narrow rim of smooth, deep-blue staining material around the nucleus. The cytoplasm did not contain granules. Structures suggestive of pseudorosettes could occasionally be recognized (Fig. 2). Interspersed between the abnormal cells were normal marrow elements.

DISCUSSION

The tumor cells in the ante-mortem bone marrow smears were not recognized as neuroblastoma cells but were interpreted as leukemic elements. Only in conjunction with the autopsy findings was the correct diagnosis established. On reviewing the literature we found out a few reports referring to bone marrow examination as an adjuvant in clinical diagnosis of neuroblastoma. Albertini and Willi[3] reported presence of lymphoid, atypical cells, often in clumps. The authors did not consider the appearance of these cells as of definite diagnostic value. They merely called them tumor cells.

Kato and Wachter[2] found in their smears aggregates of large, immature cells, often forming syncytial masses and arranged in mosaic pattern. They reported the protoplasm of these cells as being finely granular and bluish. The nuclei were described as large, with uniformly granular chromatic pattern, staining purple with May-Grünwald-Giemsa stain. Nucleoli were rare. These authors expressed the belief that the aggregates of tumor cells in the bone marrow smears correspond to pseudorosettes in histological sections and that such findings are indicative of neuroblastoma although caution is indicated. A similar point of view was adopted by Hooft and Compernolle.[4] Fanconi[5] also reported a case in which a diagnosis of neuroblastoma was established by marrow

studies. Luhby and Diamond[6a] in a recent paper which unfortunately has not been published in extenso,[6b] emphasized the occurrence of clusters and "pin-wheel" mosaic of cells, resembling psuedorosettes. Also occurrence of syncytial masses was noted. These authors believe that a reliable presumptive diagnosis can be established on the basis of the cytological pictures of bone marrow smears.

In the present case the bone marrow findings corresponded to those of Kato and Wachter as well as Luhby and Diamond. The occurrence of conglomerates of anaplastic tumor cells in the form of mosaics was noted. A comparison of the post-mortem findings with the appearance of tumor cells in the clinical bone marrow smears indicates that the clusters of tumor cells most probably correspond to pseudorosettes. However, the identity of the latter could not be convincingly established in the smears either by us or by other authors.

As to the occurrence of syncytial masses mentioned by Kato and Wachter and Luhby and Diamond, the present authors believe that this is possibly an artefact due to the great friability of the anaplastic tumor cells. No true syncytial formations were found either in our smears or in histological sections. To the best of our knowledge no occurrence of syncytial formations has been reported in histological sections of the malignant tumors under discussion.

It can be stated that occurrence of clumps of anaplastic cells in bone marrow smears of infants and children should direct the attention toward a possible existence of a malignant tumor originating in the sympathetic nervous system. Examination of slides under a low magnification will more easily reveal the presence of mosaic-like clumps of cells. A definite histological diagnosis of neuroblastoma or sympathicogonioma can, however, only be established if presence of psuedorosettes is demonstrated by biopsy.

In the differential diagnosis, the acute leukemia, particularly chloroma which can have a similar clinical course, should be considered. The anemia, associated with the usually normal distribution of the white blood cells in the peripheral blood and the described striking bone marrow changes should, however, give the clue as to the identity of the underlying disease.

SUMMARY

A case of neuroblastoma is presented. Criteria for a presumptive diagnosis of this tumor on the basis of bone marrow smears are reviewed.

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HYDROCEPHALIC DISTURBANCES DURING STREPTOMYCIN THERAPY OF TUBERCULOUS MENINGITIS. (Monatsschrift für Kinderheilkunde, Berlin, 99: 292, Aug. 1951). This paper reports on air encephalography in 52 children with tuberculous meningitis. The introduction of small quantities of air is usually adequate, especially if chief emphasis is placed on fluoroscopy. A rather severe dilatation of the ventricle system was observed in 41 of the 52 children. If treatment is begun early or in cases that are rapidly fatal, the hydrocephalus is usually slight or is completely absent. The primary localization of the disease process seems to be of particular importance for the absence or the late appearance of hyrocephalic dilatation. This is demonstrated in several examples. Asymmetry of the dilated lateral ventricles was relatively frequent. The frequent concurrence of severe hydrocephalus and primary atrophy of the optic nerve seemed especially noteworthy. In addition to inflammatory hypersecretion a disturbance of the resorption must be held responsible for the development of the hydrocephalus; this could be proved with the aid of the iodine test. The extent of the hydrocephalus plays an important part in the prognosis of tuberculous meningitis. Retrogression of dilated ventricles was observed in three cases. The author calls attention to the possible dangers of encephalography in cases of tuberculous meningitis and stresses the need of careful selection of cases. If air is introduced during the interval when no treatment is given it is advisable to give streptomycin concurrently.—*Journal A.M.A.*

TWO NEW FUNGICIDES FOR COCCIDIOIDES IMMITIS*

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Two new drugs for coccidioides immitis are herein introduced. They are called Rimocidin and Stilbamidine. Though in vitro studies were done with both drugs, the latter has been used in vivo in cases of blastomycosis by Schoenbach et al.[1]

Fig. 1. Luxurious growth of coccidioides shown in control. Complete inhibition with 75 micrograms per milliliter of Stilbamidine, and growth again at 7.5 micrograms per milliliter.

Stilbamidine and Rimocidin were put in Sabouraud's media in Di-(B-Hydroxyethane Sulfonate). Rimocidin[2] is derived from a culture broth of Streptomyces rimosus as is terramycin. It is recovered from fermentation broth by extracting the mycelium with n-butanol. "Its sulfate crystallizes from aqueous methanol as large

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fragile plates containing 7 per cent water of hydration." It has fungicidal properties in such low concentrations between 1 and 10 micrograms per milliliter on such pathogenic fungi as Histoplasma capsulatum, Blastomyces brasiliensis and dermatitidis, Trichophyton sulfureum, Sporotrichum schenckii, Hormodendrum compactum, Cryptococcus neoformans, Phialophora verrucosa, Trichophyton violaceum and Candida albicans. "The acute intravenous LD_{50} of Rimocidin in the mouse is approximately 30 mg. per kg. of body weight."

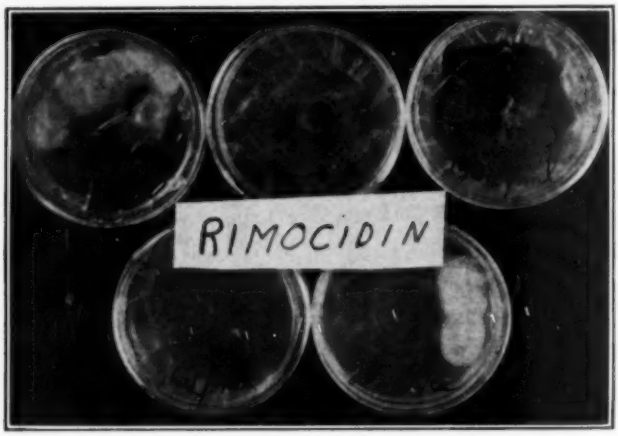

Fig. 2. Control shows luxurious growth of coccidioides whereas complete inhibition at 25 micrograms per milliliter of Rimocidin and reappearing of growth at 2.5 micrograms per milliliter.

Stilbamidine and Rimocidin were put in Sabovraud's media in various low concentrations. The inoculum was a loopful of pus from a coccidioidal abscess. The petri-dishes were sealed with Scotch tape and placed at room temperature and read in five days and daily thereafter. The controls grew coccidioides as expected. Rimocidin inhibited completely the growth of coccidioides immitis in a concentration of 25 micrograms per milliliter and Stilbamidine inhibited the growth of coccidioides at 75 micrograms per milliliter. The photographs reveal these findings nicely (Figs. 1 and 2).

Drugs found to inhibit coccidioides immitis in vitro and some in vivo are herein listed to bring this study up to date (Table 1).

TABLE 1.

Drug	Inhibiting Conc. (mcg/ml)	Uses Locally	Uses Systemically
ACTIDIONE[2] (Irradiated strepmycin gresius)	greater than 1000	as ointment slightly helpful	too toxic; some success on disseminated cases
PRODIGIOSIN[4] (Dye of Serratia marceaens)	10	?	clinical report not published as yet
CHLOROMYCETIN[5] (chloramphenicol)	greater than 2000	not helpful	not helpful
SODIUM CAPRYLATE[6] (Salt of caprylic acid) $CH_3(CH_2)_6COOH$	between 19 and 150	Useful as an ointment and irrigation solution	not helpful I. V. or orally
ETHYL VANILLATE[6] $C_{10}H_{12}O_4$	375	not too helpful	encouraging, clinical report not published yet
FRADICIN[6] (Factor X of Streptomyces fradiae)	1.2	slight in low conc.	too toxic; not given a clinical trial
THIOLUTIN[6]	1.3	not tried	not tried
PROTOANEMONIN[7] (lactone of acetylacrylic-extract of buttercup)	5	not tried	too toxic

CONCLUSION

Two new fungicidal drugs were studied in vitro and were shown capable of inhibiting coccidioides immitis. The aromatic diamidine, Stilbamidine, has been used successfully in blastomycosis and we hope to give it a clinical trial in some disseminated coccidioidal cases and we soon hope to try Rimocidin for the same type of infection too.

Personal thanks are extended to Merck and Co. and the Chas. Pfizer Co. for their contributions of their drugs to this problem.

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PEDIATRICS HALF A CENTURY AGO

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

RHEUMATIC CARDITIS IN CHILDREN*

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The title of this paper was selected because of the prominence of two features of heart disease in children. First, the fact that the majority of cardiopathies in the young are of rheumatic origin; and second, that inflammations of the heart in children, where more than transitory, are seldom confined to either the covering, lining or mural tissues of that organ, but involve the one as well as the other. Therefore the term "Carditis" is appropriate in considering, somewhat generically, the inflammations of the heart in children.

As to the frequency of rheumatic heart lesions, they are acknowledged to be more common in children than in adults. Statistics vary greatly. According to West, 61.3 per cent of the cases of rheumatism in children show endocarditis, while de Gassicourt gives the percentage as 81. In this connection we must remember that typical attacks of rheumatism are not common in children under ten years of age, and that they are rare before five.

The acquired forms of heart disease in children usually show definite causes; the majority are due to infection of which rheumatism takes first place. The upper respiratory tract is a frequent and important port of entry for infections which may result in heart inflammations, and these, as Packard has pointed out, may be other than rheumatic. Toxic muscular disease, primary as far as the heart is concerned, is rare except in connection with parenchymatous nephritis and certain acute infections, yet their occurrence must be admitted in connection with rheumatic

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At the time of writing this paper the author was Professor of Clinical Medicine, Medical Department of University of Illinois, Professor of Internal Medicine, Chicago Polyclinic, etc.
Reprinted from ARCHIVES OF PEDIATRICS, 24: 674-682, 1907.

infection. Diphtheria, tuberculosis, and influenza are not under consideration, though we may note that the latter is much more rare in children than in adults. Muscular degenerations of the heart and vessels are not present, hypertrophy is rapidly effected, and, therefore, overstrain is a less serious danger than with the adult.

If we regard rheumatism as an infection, then rheumatic heart disease must be considered as due to the direct effect of the organisms of this infection and of their poisons upon the heart structures, endocardial, pericardial and myocardial. We may be ready, with Poynton and Payne, to regard the lesions as due to a specific bacterium, or we may regard the infection as of a somewhat protean nature. In either event, the long recognized features of heredity, predisposition, personal vitality and resistance, exposure to dampness and humidity, malassimilation, overcrowding in houses and in schools, gain instead of lose in importance.

Unquestionably, the most important factors in the etiology of heart disease in early life are local disturbances in the upper respiratory tract, and overcrowding of children in tenement dwellings and in public and private schools, especially in those where impure air and imperfect ventilation obtain.

The pathology of rheumatic carditis in children is rendered comparatively simple, for the various changes from the almost benign process showing swelling and exudation without destruction of tissue to the most virulent infection showing rapid multiplication of bacteria and the destructive tissue processes characteristic of the socalled malignant type of disease are readily explainable. The doubt at present is not as regards the infective nature of certain forms of endocarditis, but as to whether and to what extent mixed infection is necessary to such a process.

It is not necessary to discuss the character of the processes resulting in incompetence or stenosis of the valvular orifices; they are readily explained by infective causes. So far as endocarditis is concerned it is important to remember that simple endocardial inflammation is not only rarely, or never, fatal during its acute stage, but also that it is quite likely to pass unrecognized at this time, as the many instances of chronic endocarditis which have not had recognized acute stages testify.

Pericardial inflammation represents a more severe type of infection, as a rule; at least the acute phase is more often serious than is the case with endocarditis. Chronic, adhesive pericarditis may be difficult or impossible of recognition, as shown by a recent case of complete synechia of the walls of the sac, of which there was not one definite sign during life, the heart being immensely enlarged because of endocardial conditions.

Myocardial changes are, I believe, more frequent than we have been accustomed to believe. In many cases the early appearance of dilatation can only be explained by assuming a damaged muscle, even though endocardial lesions be present. These muscle changes, by whatever name they may be called, are more marked in severe cases of pericarditis, yet they do not depend upon extension even though most pronounced in the vicinity of the visceral pericardium, for they may be found in patches distributed through the ventricular wall along the smaller blood vessels, and may be present even without pericarditis.

Poynton maintains that fatty changes are not entirely due to nutritional disturbances of the circulation, and can be produced in a few days in the monkey by intravenous inoculation of the diplococcus. The nature of these processes, the factors controlling their frequency and severity and the reasons why they vary so much in cases apparently of the same general character, are obscure matters at present, but they are of the utmost practical importance.

The clinical history of rheumatic carditis is an interesting study. As a profession we have been woefully neglectful of that class of manifestations which are premonitory to actual cardiac disease in children. In view of the extreme importance of preventative measures, these suggestive symptoms carry a double meaning.

Among these symptoms we have all the various ways in which insidious rheumatic tendencies may manifest themselves, such as imperfect nutrition, transitory fever, growing pains, epigastric pain, nervousness, night terrors, chorea, myalgia, arthritis, tonsillitis, epistaxis, slight lobular pneumonia, pleurisy, small glandular nodules, erythema multiforme, irregular bowels; these may all be forerunners of actual rheumatic heart disease.

Subjectively, children are apt to present obscure signs, pain and

restlessness being relatively slight. Dyspnea, however, is more important in a child than in a grown person. But no one symptom is as important in a child as that same symptom would be in an adult, and we should hesitate to form an opinion on a single physical sign. Judgment based on moderate changes in the area of dullness, or on certain characters of bruits, is especially liable to be erroneous when the subject is a child.

In those instances where the heart is attacked early and severely, pain, dyspnea, nervous excitability, and the thumping impulse of the heart will call our attention at once to the fact of cardiac involvement. But in many instances, I was going to say in the majority, our attenton is drawn away from the heart by rheumatic manifestations elsewhere, or by some of the lesser, irregular manifestations of rheumatism, and the acute stage of the cardiac trouble passes by unnoticed. My personal observation has been that, of the patients from twenty to forty years of age who exhibit chronic endocarditis of undoubted rheumatic origin, the majority will deny any knowledge of the acute period of the disease, and generally of any rheumatic manifestation recognized by them as such. Herein lies the necessity for routine examination of the heart in children suffering from any condition suspicious of rheumatic possibilities.

Objectively, we are too much given to attributing increased pulse rate to fever, and, in the absence of any bruit or friction sounds, passing the heart as uninvolved. The heart muscle in children accommodates itself to pressure by dilating the chambers much more quickly than in the adult, even though its tissue be uninvolved, and it recovers from this condition with equal promptness. In this latter faculty rests the potential possibilities of the heart of youth in withstanding overstrain. Dilatation of the heart in children is, therefore, one of the earliest and most valuable signs of cardiac trouble, one which may be present without any other sign except a rapid pulse. But the pulse is a much more uncertain guide in children than in adults.

It is true that with dilatation there will be modification of the heart sounds, as a shorter, sharper first sound at the apex, and intensification of the second sound at the base, but these may not be so evident to some ears as would an increased area of cardiac

dullness and a slightly displaced apex impulse as determined by careful palpation and percussion with the trunk in both the erect and recumbent positions, being careful that the body is neither turned nor inclined to either side.

While it is true that this condition of dilatation may occur from purely physical causes and cannot be regarded in itself as evidence of any form of carditis, it is, nevertheless, an early sign of the latter condition when such is present, and I believe it is not claiming too much to maintain that proper therapeutic measures at this time will often modify the course of rheumatic carditis and may prevent the development of organic changes which would be permanent.

It is not necessary to discuss the diagnostic features of valvular lesions, but we should beware of expecting or depending upon classical features during the acute stage.

In mitral disease, the first sound becomes short and ill defined, and the murmur, if present, may be inconstant. A to and fro sound simulating aortic murmurs may be present in mitral lesions at first. A prediastolic or diastolic apical murmur during the acute stage is not always positive of stenosis in children. The second sound may, apparently, be reduplicated in mitral disease.

With aortic lesions, which are rare in children, the first indication of incompetence is a somewhat gradual weakening and disappearance of the second sound, which is then replaced by the characteristic murmur.

Acquired lesions of the right side are exceedingly rare, but I have observed an instance, elsewhere reported (Clin. Rev., April 1906) of slight pulmonary stenosis developing during an acute phase of chronic endopericarditis, and diagnosed during life by its characteristic murmur.

Pericarditis, while a most serious condition, is likely to cause errors in prognostic judgment because transitory attacks, even though marked by distinct friction, may be entirely recovered from, while a slow organizing type of inflammation without definite symptoms may lead to irreparable injury. Again, myocarditis and endocarditis may cause symptoms simulating pericarditis, while the latter may be absent.

In pericarditis the temperature is higher than with endocarditis, the pulse more rapid, excitable and possibly irregular. It varies much in rhythm and tension. The heart action is excitable and

forcible. The first sound is short and sharp, and if there is friction and a bruit the combination is quite unlike any other. Precordial pain is often well marked. Friction may be single or double. It is best heard at the base or just above, or about the level of the third interspace or the fourth rib, between the left edge of the sternum and the left parasternal line. It is not always readily distinguished from endocardial sounds.

You are familiar with the physical signs of a considerable effusion into the pericardial sac, a condition not common in children with rheumatic carditis, yet more often met, I believe, than some authorities think. The diagnostic difficulty seems to be, and most of the errors I have observed have been, in distinguishing between cardiac dilatation and effusion. The area of dullness of the former may be, when considerable, difficult to distinguish from that of effusion. Ewart's sign, Rotch's sign, and the distinction between the limit of the lower left angle of dullness and the inner and higher position of the apex beat would be definite means of differentiation were it not for the fact that the two former may be present with a dilated heart, and the latter is usually difficult to determine. The shortening and weakening of the first sound in dilatation are often mistaken for the interference with the appreciation of the heart sounds by an effusion, while the diffuse character of the impulse of a dilated heart may resemble the lifting motion shown with effusion. I have several times been asked to aspirate a pericardial effusion, and found only a dilated organ. A rapidly disappearing effusion might, of course, account for this, but in some instances I was convinced that no effusion of moment had been present.

It is very difficult to separate the symptoms of myocardial changes from those of endo- or pericarditis. This is especially true of the most common type, in which the latter tissues are but slightly affected, and in which myocardial damage is not immediately severe. If, however, we can exclude pericarditis and any marked endocardial involvement, or it is evident that the degree of cardiac weakness is not explainable by the severity of the endocardial condition present, the symptoms must be attributed to changes in the myocardium. These patients show anemia, restlessness, dyspnea, even when at rest, rapid and irregular pulse, and a moderately dilated heart which remains large for a long time with marked variations in pulse rate and rhythm.

Another type of acute rheumatic myocardial disease, fortunately rare, because of its fatality and the danger of sudden death, is marked by a temperature around 101° F., a pulse from 120 to 150, rapid breathing, precordial pain, pallor, syncope and vomiting. There is slight edema, a diffuse impulse, enlarged area of dullness in all directions, a short first sound, accentuated second sound, and there may be a systolic bruit very low pitched and difficult to hear.

The prophylaxis of rheumatic carditis in children grows in importance with our appreciation of the infectious nature of the disease. A better knowledge of the avenues of infection and of the laws which control its occurrence promises untold benefit to the youth of coming generations. In many instances our complete impotence to stay the development of incurable lesions of the heart brings all the more forcibly to us the necessity of preventing the initial infection. We must, therefore, give closer attention to the conditions contributing to rheumatic infections. Most of these have been already enumerated. I wish, however, to lay special stress on two factors of importance. The first of these is the local condition of the upper respiratory tract, especially of the mucosa covering the turbinates, the state of the tonsils, and the adenoid conditions of the vault. Even in children who will not submit to operative measures when such are advisable, the daily use of a gargle and nose wash and prompt local attention to acute nose and throat infections will prevent much subsequent trouble.

The second factor of special importance is the opportunity for infection furnished by unsanitary dwellings and in overcrowded and imperfectly ventilated school houses. Mitigation of the former entails concerted endeavor by the forces of municipal sanitation and the philanthropic tendency of social economics, which it is not our province to discuss, but, in view of the amount of public monies expended on education and the direct interest therein of every citizen of family, it is evident that the municipal department of public health should exercise a direct supervision over the topography, architecture and conditions of attendance of our public schools with a view to limiting the opportunities for infection, instead of confining, as at present, their attention to the exclusion of suspicious subjects.

The general hygiene of childhood and the consideration which should be given systematic conditions likely to favor the occurrence of infections of any kind are matters the importance of which can only be alluded to here. Their management embodies measures with which you, as pediatrists, are more familiar than I, but while I do not wish to minimize the attention to be given to children of rheumatic parents, I would call attention to the fact that the infectious nature of rheumatism raises the physical condition as related to resistance to infection above the possibilities of hereditary predisposition, and, therefore, diet, fresh air and exercise assume an importance beside which the old beliefs of the dangers of meat diet, outdoor exposure and overstrain in such children are entitled to revision.

The treatment of acute rheumatic carditis embraces measures about which there is some divergence of opinion. The value of rest, however, is generally emphasized, and yet I believe this measure is not sufficiently enforced. Holt is quite decided as to the value of prolonged rest, and I do not think he overstates it. It is always difficult to maintain rest with a child after pain and dyspnea have subsided, but it should be insisted on with the recumbent position until the heart does not increase more than four or five beats per minute with assuming the erect posture, whether the time necessary be three weeks or six. When the child begins to get about on its feet a rest of from one-half to one hour after meals should be insisted on.

When prolonged rest has been necessary the period between this and voluntary movements can be utilized with passive movements. Voluntary movements should be undertaken gradually and should be governed by much the same rules as in adults. The value of fresh air and change of scene should be kept in mind.

The medicinal treatment of the acute period of the attack brings up the question of salicylates. On the one hand we have the positive advocates of this drug as represented by Lees, who uses 10 grains of the sodium preparation every two hours during the day and every four hours at night, later, increasing to 30 or even 40 grains, if necessary. He controls its depressing action on the respiratory center, as represented by air-hunger, by giving twice as much bicarbonate of soda.

On the other hand are those who, like Poynton, believe that

salicylates are only palliative and should be given in small doses. These, in cases of arthritis, will be from 5 to 10 grains every three hours. He does not believe it is antidotal in cardiac rheumatism.

Salicylates are, in my experience, effective. Both primary attacks and relapses usually respond to their use more or less promptly. In children from five to ten years old I seldom find it necessary to use more than from 5 to 8 grains every four hours, and I always combine it with an alkali, as sodium bicarbonate or the acetate of potash, or both, for the drug is then more quickly eliminated and its bad effects are lessened. It should be given in decreasing doses for a short time after active symptoms, especially fever, have subsided. I would also call attention to the value of salicylate of soda, both as a gargle and internally, in rheumatic sore throats in children.

After convalescence is established small doses of iodids are beneficial, iodid of sodium or strontium, or hydriodic acid preferred.

Strychnia is a remedy to be used with caution, and only for definite indications, such as a rapid, weak pulse, or for collapse after exertion. Children do not bear strychnia well, and their hearts are readily excited by it.

Digitalis, in the acute stage, should only be used if the heart is dilated and its exertion is out of proportion to the condition of the circulation. We must be careful not to mistake an excited heart for a weak one. The tincture is the most available preparation for children. It should not be discontinued abruptly.

Alcohol is useful in exhaustion or threatened collapse, but I have found very few occasions for its use.

When fever is high, the heart excited, and there is restlessness, from 5 to 10 grains of bromid of sodium with a quarter of a drop of tincture of aconite and a teaspoonful of sweet spirits of nitre every two hours will be found useful. If pain is severe codein and bromid of soda are beneficial.

The local use of the ice bag is efficient for two purposes: to quiet an excited, thumping heart, and to relieve pain, as in pericarditis. The ice should be fine, the bag should be arranged so as not to bear too heavily on the chest wall, and it should be removed if there is a sudden fall of temperature or any signs of collapse. Hot water bags should be placed near the lower extremities, if the limbs are cold, while the ice bag is in use.

Local or general bleeding is a measure only to be used under the exceptional circumstance of a dilated right side, and then with great caution.

Any measure which worries or excites the child is not worth continuing, and any avoidable disturbing influence should be carefully obviated.

There are many measures as to diet, general and symptomatic management, and after-care, for whose lack of consideration I excuse myself on the ground that in these the members of this society are more proficient than I am.

GLYCOPRIVAL MALNUTRITION IN INFANTS. (Monatsschrift für Kinderheilkunde, Berlin, 99: 283, Aug. 1951). Clinical observations are reported on infants in whom nutritional disturbances were accompanied by considerable reductions in blood sugar values and by a fall in temperature, which at times caused severe collapse or collapse-like crises. Such cases of glycoprival inanition are not caused by one factor alone. This is proved by the observation that not every case of dystrophy resulting from nutritional disturbances is accompanied by a reduction in blood sugar. The fact that the oral administration of sugar is rapidly followed by a lasting increase in the blood sugar content, whereas intravenous administration of dextrose after a temporary increase of about an hour and a half is again followed by a rapid decrease in blood sugar, seems to indicate the importance of the liver in these processes. As a result of severe depletion in its glycogen stores the liver seems no longer capable of supplying the energy requirements of the peripheral parts of the body by way of the blood sugar. This glycogen deficiency can be traced to a reduced absorption of carbohydrates as the result of prolonged dyspepsia. Apparently, an inhibition of the phosphorylation processes plays a part in the absorption and metabolism of carbohydrates. This concept is further supported by Diehl and Thaddea, who assume that the weakness or toxic impairment of the adrenal cortex in Addison's disease is a sequel of chronic gastrointestinal disturbances. The blood sugar crises in the course of severe dyspepsia, or glycoprival inanition, make it necessary to investigate the blood sugar values in all severe nutritional disturbances.—*Journal A.M.A.*

DEPARTMENT OF ABSTRACTS

PARROTT, R. H.; ROSS, S.; BURKE, F. G. AND RICE, E. C.: HERPANGINA. CLINICAL STUDIES OF A SPECIFIC INFECTIOUS DISEASE. (New England Journal of Medicine, 245:275, Aug. 23, 1951).

The authors report a study of 22 cases of herpangina in children ranging in age from 6 months to 8 years, fourteen of them being between 1 to 4 years of age. The disease has a sudden onset with a rapid rise in temperature in 24 to 36 hours to 101° to 105° F. lasting 1 to 4 days. Sore throat, anorexia and dysphagia were frequent symptoms. The throat lesions are characteristic. These consisted of grayish-white papulovesicular lesions about 1 to 2 mm. in diameter, with a surrounding areola of erythema. The lesions rupture eventually, assuming an ulcerated appearance with a greyish-yellow appearance, the erythema zone becoming more intense. The lesions are usually found on the anterior tonsillar pillars although they are occasionally found on the soft palate, uvula and tonsils. The disease is benign, running a self-limited course without complications. Viruses were recovered from 86 per cent of the cases. These viruses were similar to those classified among Group A "Coxsackie" viruses.

MICHAEL A. BRESCIA, M.D.

BRIGGS, J. N. AND DOXIADIS, S. A.: THE Q-T INTERVAL IN RHEUMATIC FEVER. (Archives of Disease in Childhood, 26:311, Aug. 1951).

The Q-T interval was measured in 112 electrocardiograms of 82 children with rheumatic fever and of 20 normal controls. The Q-T interval was above the maximal normal limit in 8 of 68 tracings taken during active rheumatic infection, in 3 of 24 tracings of children with inactive rheumatic heart disease, and in none of the tracings obtained from the controls. There was a significant difference between the mean Q-T interval of all the children with active or inactive carditis and the control group. It is concluded that rheumatic infection may prolong the duration of the electrical systole, but the degree of this change is such that it is of diagnostic value in only a few cases.

AUTHORS' SUMMARY.

DIETRICH, H. F.: TETANUS NEONATORUM. REPORT OF TWO CASES WITH OMPHALECTOMY AND RECOVERY. (Journal American Medical Association, 147:1038, Nov. 10, 1951).

Two cases of tetanus neonatorum are reported; in both, the umbilicus was excised as the probable source of infection. Both patients received moderate doses of intramuscular tetanus antitoxin and liberal doses of sedatives. They recovered, and it is suggested that omphalectomy may be a reasonable adjunctive therapy in this disease. Further trial of this essentially benign surgical procedure, with strict attention to established therapeutic regimens, should provide a significant answer as to its value.

AUTHOR'S SUMMARY

BERRY, L. H.: MEDICAL COUNSELING CLINICS FOR YOUNG NARCOTIC ADDICTS. (Journal American Medical Association, 147: 1129, Nov. 17, 1951).

Narcotic addiction among juveniles and young adults has reached epidemic proportions throughout the nation. An international underworld system controls the sales promotion and distribution of the drugs. Medical prevention and follow-up care is a reasonable community responsibility of the medical services and allied organizations. Withdrawal of narcotic drugs is best carried out in a hospital, but about 4 out of 5 addicts return to drug use after the best available treatment. A plan of long-term regional counseling and rehabilitation clinics is presented.

AUTHOR'S SUMMARY.

KAHN, H. A.: CHANGING CAUSES OF DEATH IN CHILDHOOD. (Public Health Reports, 66:1246, Sept. 28, 1951).

Cardiovascular disease and cancer now cause more deaths among children of school age in the United States than all the infectious and parasitic diseases combined. Within recent years the long-term trend of decreased mortality from infectious diseases has resulted in the change. The infectious diseases are no longer more frequent than other diseases as a cause of death among school-age children. In 1948, cardiovascular disease and cancer deaths totaled 4,514 in the 5 to 19 years age group, while the infectious and parasitic diseases accounted for 3,990 deaths in the same age group.

MICHAEL A. BRESCIA, M.D.

BOOK REVIEWS

INFANT DEVELOPMENT: THE EMBRYOLOGY OF EARLY HUMAN BEHAVIOR. By Arnold Gesell, M.D. Cloth. Illustrated. Pp. xi+108. Price $3.50. New York: Harper and Brothers, 1952.

Pediatrists, psychiatrists and physicians generally have complained that Gesell's writings were too detailed and technical for their purpose. Here is the answer. In a small book, illustrated with arresting photography, the philosophy and research undertakings of the Gesell group are set forth. The implications of the studies are shown by vivid examples relating to developmental diagnosis and its significance as a tool in the supervision of the child's mental and physical well-being. To the uninitiated, growth and development frequently mean merely getting bigger and developing more ability. But growth, either physical or mental, is not this simple; rather it is intricate and devious. The physician who diagnoses and treats children and advises their parents, cannot do his job adequately without an understanding of the laws of growth,—the balance and imbalance which the child undergoes,—the stages of development,—their normal and abnormal deviation,—their recuperative powers,—and their individuality in behavior as well as in body. For years, Gesell has been insisting that the physician has a responsibility for the child's mental as well as his physical health. But this responsibility cannot be discharged without as great a knowledge of the child's mental and emotional growth as the physician has of physical growth. This primer will introduce Gesell's thesis and clarify the significance of the Gesell studies which may have been misunderstood. To those who have followed Gesell's writings in detail, the book will crystalize their understanding. To all, it will offer an inspiring vision of the plan as well as the force with which early human behavior emerges.

HELEN THOMPSON, PH.D.

ALLERGY IN RELATION TO PEDIATRICS. By Bret Ratner, M.D. Cloth. Pp. 228. Price $3.75. St. Paul and Minneapolis: Bruce Publishing Company, 1951.

This book represents a panel discussion by some 16 men interested in the field of allergy in special relation to pediatrics which took place in Chicago in April 1949. In the opening discussion on the Genesis of Allergy in Infancy and Childhood, B. Ratner

cautions that the practice of overfeeding infants, and the present vogue of introducing many new foods very early in infancy might be a sensitizing factor. The chapter by M. M. Peshkin on the Critical Evaluation of Diagnostic Tests for Sensitization in Infancy and Childhood is well worth reading and he concludes: "To fix the responsibility in an allergy syndrome requires a selected series of allergenic skin and other tests accurately performed and properly interpreted, together with a thorough history, physical examination and careful study of the case, extending over varying periods of time." The difficulty of further evaluating skin testing is emphasized by L. W. Hill in his discussion of the Significance of Skin Tests in Respiratory and Dermatologic Allergy when he stated that "in asthmatic children many positive skin tests to foods are obtained. A high proportion of these (probably 75 per cent) are entirely without etiologic significance." The importance of using breast milk in infant feeding is emphasized by W. A. McGee (Allergy of the Intestinal Tract) and R. H. Todd (Prophylaxis of Allergy in Children) the latter stating: "If we can start our newborn on breast milk, we will avoid one of the most common allergens—cow's milk." The brief chapter on Maternal Rejection in Allergic Children by D. W. Baruch and H. Miller highlights the importance of the psyche even in such a disturbance as allergies which were thought to be purely due to foreign substances or reactions to foreign substances. MICHAEL A. BRESCIA, M.D.

THE BATTLE FOR MENTAL HEALTH. By James C. Maloney, M.D. Cloth. Pp. 98. Price $3.50. New York: Philosophical Library, Inc., 1952.

The author at the outset defines mental health as one who competently evaluates and relates himself to living and non-living objects and accurately measures time and space. Mental health connotes emotional, physical and intellectual adequacy. The text then wishes us to believe that Americans are losing the battle for mental health by a presentation of varied psychiatric and crime cases. Our American culture receives much attention throughout the book as a definite force hastening our breakdown. This text is an appeal for urgent need of the Cornelian Corner and permissive method of child training. Our present parent-child relationship is woefully inadequate and poorly encouraged by all concerned whether obstetrician, pediatrician, maternity nurse or hospital

superintendent. Dr. Maloney feels that rooming in a room of bright and pastel shades and other material conveniences with attending personnel from doctors to janitors selected from those who are appropriately spontaneous, temperamentally suited and properly educated in the natural ways of a mother with her newborn child would greatly aid in our battle for mental health.

H. Fruchter, M.D.

Healthy Babies. By Josephine Hemenway Kenyon, M.D. and Ruth Kenyon Russell, M.D. Cloth. Pp. 306. Price $3.00. Boston: Little, Brown & Co., Revised Edition 1951.

Described as "A Complete Handbook for Modern Mothers," this book is precisely that. Young parents and prospective mothers, besieged by articles in the public press or confused by advice from well-meaning friends, can find comfort in the obvious stability of this book. They will take reassurance from the fact that the authors, both of them mothers as well as physicians, offer as their credentials not only scientific training but personal experience. Every new need or anxiety has been anticipated. For those hopeful of raising a family there is information concerning periods of fertility and infertility, times for conception, etc. For the newly pregnant woman, warning is given of all the possible discomforts she may experience, with suggestions for relieving or preventing them. (The book may be her best friend here because as yet not sure the pregnancy is "real" she may be loathe to discuss her symptoms with anyone, even a doctor). For the parents of a newborn child there are guideposts to his needs and behaviors up through the first three years of life. The frantically worried mother and father will find first aid and health care hints covering all emergencies. The 1951 Revision brings several welcome additions, in particular fuller information concerning the premature child and the child slow to develop. In each area the individual parent will find solace in discovering that her particular problem is not unique. On the other hand, there will be infinite psychological value in noting triumphantly where she has been spared a possible pitfall! Never a substitute for a doctor's advice, "Healthy Babies" may yet be highly recommended as a useful and handy supplement. It offers the parent content which is accurate, form that is clear, and a style warm and readable.

Maureen H. Haberer, M.A.

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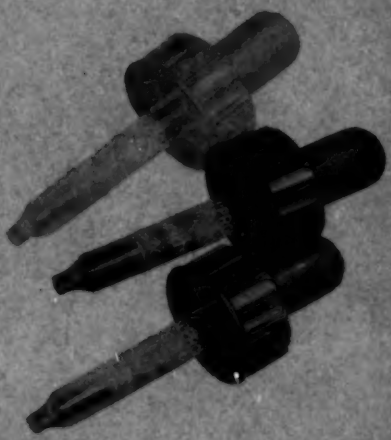

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